REMARKS

Claims 40, 42, 44, 46, 56-58, and 61 are presently pending. The Examiner has again maintained the obviousness rejections from the previous Office Action that are rebutted in the following order:

I. Rejections Under 35 USC §103(a)

A. Claims 40 and 61 are allegedly unpatentable over United States Patent No. 4,873,316 Meade et al., in view of Jorgensen et al., *J Biol Chem* 262:6729-6734 (1987), Seegers et al. *Blood* 5:421-433 (1950), and further in view of van Cott and Velander *Expert Opinion on Investigational Drugs* 7:1683-1690 (1998), and previously cited Velander et al. *Proc. Natl. Acad. Sci. USA* 89:12003-12007 (1992)..

B. Claims 40, 42, 44, 46, 56 and 58 are allegedly unpatentable over United States Patent No. 4,873,316 Meade et al., in view of Jorgensen et al., *J Biol Chem* 262:6729-6734 (1987), and further in view of Le Bonniec et al., *J Biochem* 266:137796-13803 (1991).

C. Claims 40 and 57 are allegedly unpatentable over United States Patent No. 4,873,316 Meade et al. in view of Jorgensen et al., *J Biol Chem* 262:6729-6734 (1987), and further in view of Seegers et al., *Blood* 5:421-433 (1950); and further in view of Le Bonniec et al., *J Biochem* 266:137796-13803 (1991).

I. The Claims Are Not *Prima Facie* Obvious

Obviousness is currently determined based upon an evaluation of the magnitude of the differences between the claimed embodiment and the asserted prior art:

> In *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 86 S. Ct. 684, 15 L. Ed. 2d 545 (1966), the Court set out a framework for applying the statutory language of § 103 ... "Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained ...

KSR v. Teleflex, 127 S. Ct. 1727, 1734 (2007). Further, the *KSR* holding only cautioned against a strict application of the "teaching-suggestion-motivation test" such that an explicit teaching is not required to be found within the cited applications. Nonetheless, *KSR* has NOT changed the

law regarding the requirement to establish a *prima facie* case of obviousness by: i) finding *some motivation* to combine the references either explicitly or implicitly, ii) finding a teaching or suggestion of all the claim limitations in the cited references; and iii) demonstrating that the references provide sufficient technical detail such that one having ordinary skill in the art would be provided with a reasonable expectation of success. *In re Vaeck*, 947 F.2d 488, 20 USPQ.2d 1438 (Fed. Cir. 1991); and *MPEP* § 2142; Establishing A *Prima Facie* Case Of Obviousness.

A. Meade et al., Jorgensen et al. and Velander et al. Do Not Teach A Composition Of A Completely Carboxylated Recombinant Prothrombin Polypeptide At A Concentration Of 0.5 mg/ml Derived From A Transgenic Mammal

The Examiner states that:

> The Examiner relied on Meade et al., for teaching an efficient means of making large quantities of recombinant protein in milk and that any protein may be produced using their method (Meade et al. cols 1-3 …

Office Action mailed Sept 2009, pg 4. The Applicants disagree. Meade et al. uses the term "large quantities" only once in an attempt to frame a goal that has advantages of cell culture secretion of recombinat protein. *Meade et al. col 1 ln 53-56.* Despite this assertion, Meade et al. failed to produce any method that, in fact, produces large quantities of recombinant protein.

> The G1 progeny produced 0.2-0.5 μg/ml of TPA in their milk.

Meade et al., col 7 ln 25-26 [emphasis added]. As such, Meade et al. identified the problem of low expression in cell culture but failed to solve the problem:

> This technique has proven be expensive and often unreliable due the variability of cell culture methods. For example, average yields are 10 mg of a milk recombinant protein per liter of culture media,

Meade et al., col. 1 ln 43-46. In fact, Meade et al. does not teach the expression of any recombinant protein at levels of 0.5 mg/ml, much less prothrombin comprising a fully carboxylated Gla domain. To this point, Meade et al. only teaches an expression level that is one-thousand times lower than the Applicant's currently claimed embodiment:

Further strengthening the Applicants argument that the primary combination of Meade et al. and Jorgensen et al. doe not teach any high level expression of a recombinant protein, the Examiner now agrees that Jorgensen et al, also does not provide any teachings relevant for high expression of a recombinant protein:

> Jorgensen et al, was relied upon for teaching that the sequence of human prothrombin was known.

Office Action pg 6. As such, the Examiner argues that Jorgenson et al should be evaluated only for the teachings of the Examiner's interest. The Federal Circuit has long since ruled that a specific teachings within a cited reference cannot be considered in isolation when determining obviousness:

> The critical inquiry is whether " 'there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination.' "

Fromson v. Advance Offset Plate, Inc., 755 F.2d 1549, 1556, 225 USPQ 26 (Fed. Cir. 1985). When Jorgensen et al. is viewed as a whole it adds nothing substantial to the basic methodological deficiencies of Meade et al. as should have been withdrawn as an asserted reference.

The Examiner further asserts Velander et al. for allegedly fulfilling the above deficiencies of Meade et al. and Jorgensen et al.:

> With regard to the limitation that recombinant prothrombin is expressed at a concentration of at least 0.5 mg/ml, the Examiner relied upon Velander et al., who teach that recombinant protein can be expressed in milk of transgenic pigs at levels as high as 1000 μg/ml (i.e., 1 mg/ml)(Velander et al. page 12005, 1st col, parag. Under "Protein Analysis", see also Figure 1).

Office Action mailed Sept. 2009, pg 4-5. The Applicants disagree and respectfully proceed to explain that the Examiner may have misunderstood the assay systems disclosed within Velander et al. In brief, the Applicants submit that the Examiner may have overlooked that Velander has reported the detection of up to 1000 μg/ml of hPC antigen:

> Protein Analysis. Antigen levels detected by ELISA using polyclonal capture ranged from 200 μg/ml to 1000 μg/ml

Velander et al., pg. 12005 1st col., para. under "Protein Analysis". Velander et al proceeds to explain that hPC antigen measurements are not equivalent to the detection of an intact, fully carboxylated, active hPC:

> The presence of different rhPC populations was also evident from the differences in antigen content detected by polyclonal and HPC4-Mab ELISAs and the presence of different immunofractions obtained using the HPC4-Mab. The HPC4-Mab binds the activation peptide of hPC at pH 7.3 and thus provides a measure of the presentation of a domain essential for conversion of zymogen hPC to active serine protease form (15). Each of the immunofractions possessed different anticoagulant activities, but activity did not correlate well with single-chain rhPC content. The most active fraction represented about 38% of the hPC antigen and contained 30% single-chain material. This suggests that a significant portion of the single-chain material contained in this fraction may be biologically active or that some heterodimeric forms are hyperactive. The lower activities of the second and third fractions may be a result of nonnative conformations or insufficient γ-carboxylation.
>
> The anticoagulant activity of protein C is dependent upon proper γ-carboxylation of the membrane binding domain that occurs in the light chain (18). To determine whether γ-carboxylation had occurred properly in rhPC, its anticoagulant activity was assayed in vitro by APTT. This assay simulates coagulation in vivo by initiating clotting in a mixture containing calcium, phospholipid membrane, and the proteins associated with hemostasis (16). As much as 38% (or 380 μg/ml) of the porcine rhPC may be sufficiently γ-carboxylated, as judged by the specific activity of immunofraction 1 by APTT relative to that of hPC. The transgenic pigs studied here had milk letdown about every hour and hence the maximum rhPC secretion rate occurred at about 1000 μg/ml per hr. The amount of active rhPC secreted by the pigs (about 380 μg/ml per hr) ...

Velander et al., pg 12007, col. 1, last two paragraphs. In summary, Velander et al. i) teaches assays for total hPC antigen, that represents 38 % active and 62% inactive hPC protein; and ii) does not teach the secretion of 1 mg/ml of a fully carboxylated recombinant protein. *See, "The Velander Declaration", ¶¶ 4-5.*

In combination, the Meade et al,, Jorgensen et al., and Velander et al. references do not teach the secretion of a fully carboxylated recombinant protein at a concentration of at least 0.5 mg/ml in the milk of a mammal. The Examiner is respectfully requested to withdraw the present rejection.

B. Seegers et al. Is Of No Help

The Examiner states that in regards to Claim 40 and 57:

> Seegers et al. teach that activation of purified prothrombin is accomplished by dissolving the purified prothrombin in a 25% solution of sodium citrate …

Office Action pg 7. The Examiner has not shown that Seegers et al. remedies the deficiencies of Meade et al., Jorgensen et al., and Velander et al. by teaching a highly expressed fully carboxylated recombinant prothrombin. Consequently, the Applicants argue that Claim 40 is patentable, thereby mooting the rejections under Seeger et al. to dependent claims.

C. van Cott et al. Is Of No Help

The Examiner states that in regards to Claims 40 and 61:

> According to van Cott and Velander, while transgenic mice were poor at gamma-carboxylating recombinant proteins, transgenic pigs were able to gamma-carboxylate recombinant proteins excreted in milk up to 0.1 g/l/h [29, …

Office Action pg 6. The Applicants submit that the Examiner has ignored the fact that van Cott et al. does not teach a full γ-carboxylation of a recombinant protein. As discussed above, this is an important distinction, as Velander et al. (i.e, cited reference 29 directly above), teaches that complete carboxylation is necessary for Protein C activity (as the Applicants' presently teach for prothrombin):

> … the mouse mammary gland was a very poor γ-carboxylator of recombinant Protein C and FIX, while the pig was able to γ-carboxylate up to 0.1 g/l/h …

van Cott et al., pg 1686 rhc – 1687 lhc [emphasis added]. Niether, Velander et al. nor Van Cott et al. teach a fully carboxylated recombinant expression at a level of 0.5 mg/ml. *See, "The Velander Declaration" ¶ 5.* In summary, van Cott et al. does not even mention prothrombin as a possible protein for expression. van Cott et al. does not provide any evidence that Protein C and Factor IX were fully carboxylated, only that γ-carboxylation in pigs is better than in mice. Third, the prothrombin expression level now recited in Claim 40 is 5 times superior to that referred to in van Cott et al. (i.e., 0.1 g/l/h = 0.1 mg/ml/h). As explained above, these superior and advantageous results overcome the Examiner's obviousness argument.

The Applicants submit that van Cott et al. does not provide sufficient teachings, such that when combined with Meade et al. and Jorgensen et al., that one having ordinary skill in the art could make and use a transgenic mammal capable of secreting transgenic prothrombin in milk at a level of at least 0.5 mg/ml.

The Examiner attempts to rebut the Velander Declaration by presenting the publication Camire et al., "Enhanced γ-carboxylation Of Recombinant Factor X Using A Chimeric Construct

Containing The Prothrombin Propeptide" Biochemistry 39:14322-14329 (2000). The Examiner is respectfully requested to note that Camire et al. was published AFTER the Applicant's priority application (PCTUS00/22616). Specifically, Camire et al. was published on the Internet as of October 25, 2000 while the Applicant's instant specification was filed on August 18, 2000, two months earlier. Consequently, Camire et al. not only is Camire et al. not prior art, but is also not a proper teaching reference.

Specifically, Camire et al. is an in vitro system as compared to the Applicant's claims that recite in vivo production within a transgenic animal. Due to the well accepted unpredictability of the biotechnological arts, Camire et al. does not show "an inherent property of prothrombin". The Examiner is respectfully requested to realize that *Atlas Powder* specifically refers to "the old composition". As Camire et al. does not disclose or suggest expression in a transgenic animal the Applicant's present "a new composition" that is not contemplated with Camire et al.

D. Le Bonniec et al. Is Of No Help

The Examiner states that:

> Le Bonniec et al. teach that prothrombin is activated by bovine factor Xa ... [and] that activation of prothrombin yields thrombin ...

Office Action pg 6. The Applicants argue that Le Bonniec et al. does not remedy the lack of a prima facie case of obviousness in view of the other asserted references discussed above. Specifically, Le Bonniec et al. does not provide any evidence teaching recombinant prothrombin in the milk of a transgenic mammal having a concentration of at least 0.5 mg/ml.

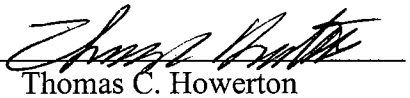
E. Conclusion

The Examiner has not provided any evidence showing that milk produced by a transgenic mammal can have at least 0.5 mg/ml of fully carboxylated recombinant prothrombin. As such, the Examiner has failed to put forth a *prima facie* case of obviousness. The Examiner is respectfully requested to withdraw all the pending rejections and pass the above claims to allowance.

CONCLUSION

The Applicants believe that the arguments and claim amendments set forth above traverse the Examiner's rejections and, therefore, request that all grounds for rejection be withdrawn for the reasons set above. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, the Applicants encourage the Examiner to call the undersigned collect at 781-828-9870.

Dated: May 17, 2010

By: 

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